Mass General Brigham
Mass General Cancer Center

CAR T-cells are preferred over transplant in 2nd line DLBCL *(most of the time)*

Jeremy S. Abramson, MD, MMSc

20th Annual International Ultmann Chicago Lymphoma Symposium

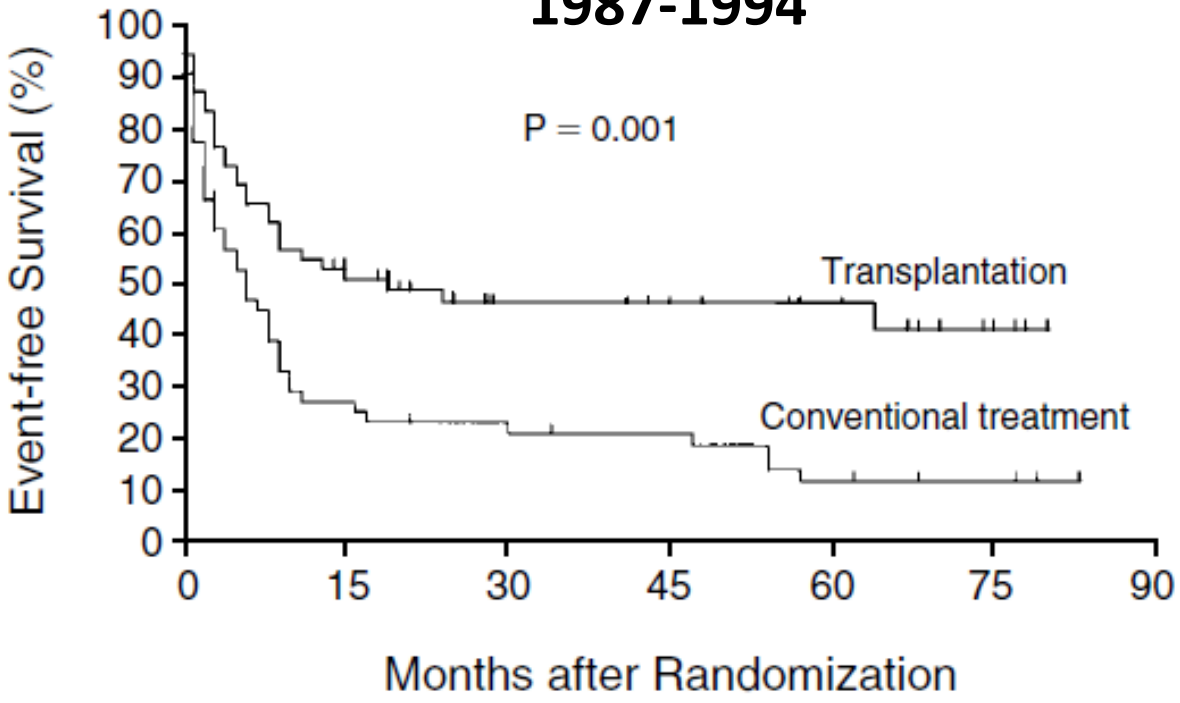
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures for Jeremy Abramson

Consulting for AbbVie, Astra-Zeneca, BeiGene, Bristol Myers Squibb, Caribou Biosciences, Cellectar, Genentech, Incyte, Interius, Janssen, Kite Pharma, Lilly, Regeneron, Takeda

A walk down memory lane…

1987-1994

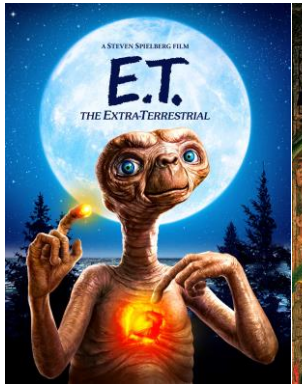


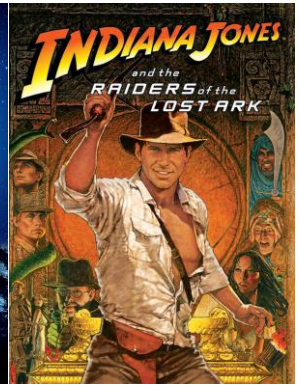
The working formulation!

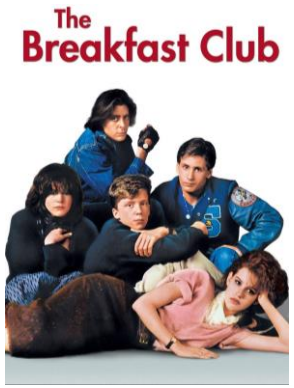
Histologic type of lymphoma
- High-grade large-cell immunoblastic
- High-grade lymphoblastic
- High-grade, with small noncleaved cells
- Intermediate-grade follicular, with predominantly large cells
- Intermediate-grade diffuse, with small cleaved cells
- Intermediate-grade diffuse, with mixed small and large cells
- Intermediate-grade diffuse, with large cells
- Other diffuse

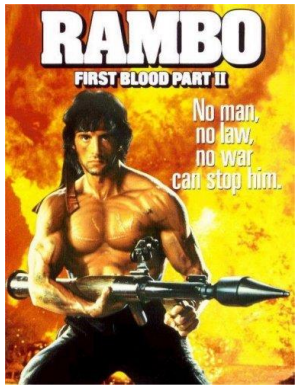
M-BACOD, MACOP-B, PROMACE-CytaBOM still in use for DLBCL (or whatever it was called back then)

Philip, et al. NEJM. 1995


A STEVEN SPIELBERG FILM
E.T.
THE EXTRA-TERRESTRIAL

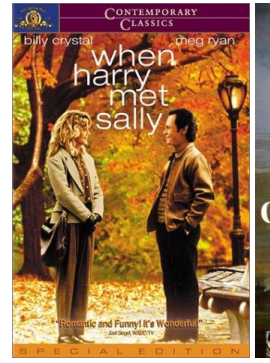

INDIANA JONES
and the
RAIDERS of the LOST ARK

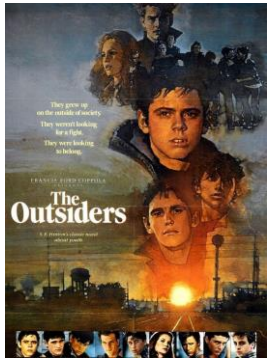

The Breakfast Club


RAMBO
FIRST BLOOD PART II
No man,
no law,
no war
can stop him.

THE 980s
STAY PUFT

ROBIN WILLIAMS
He was their inspiration. He made their lives extraordinary.
DEAD POETS SOCIETY
A PETER WEIR FILM

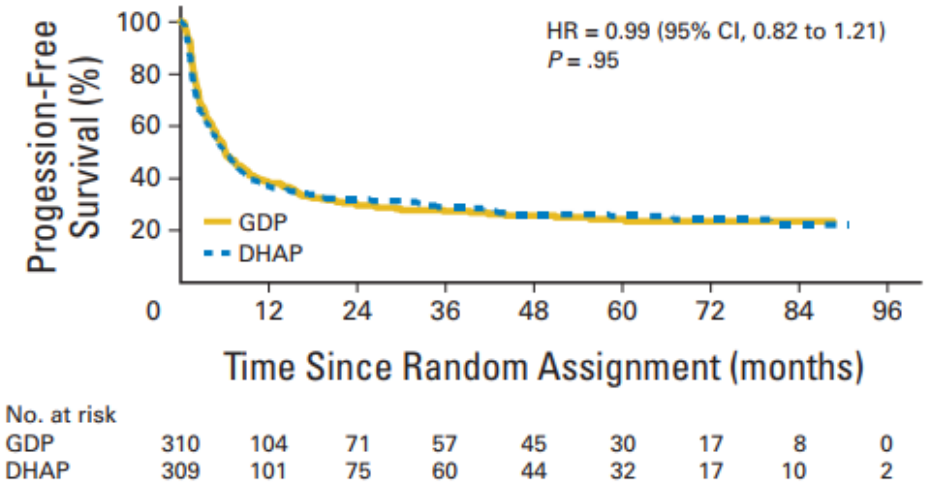

CONTEMPORARY CLASSICS
billy crystal
meg ryan
when harry met sally
SPECIAL EDITION


The Outsiders

A ROB REINER FILM
THE PRINCESS BRIDE
FIGHT. DIE. LOVE... AS YOU WISH

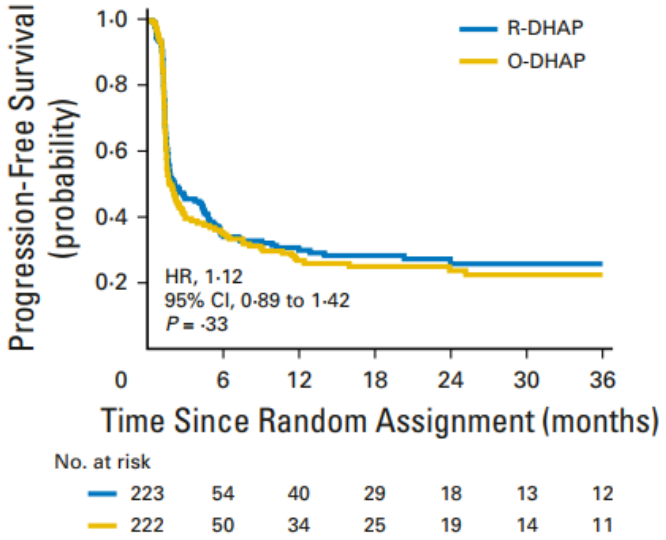
Platinum based chemo and ASCT Just Ain't What it Used To Be…

NCIC-CTG LY.12



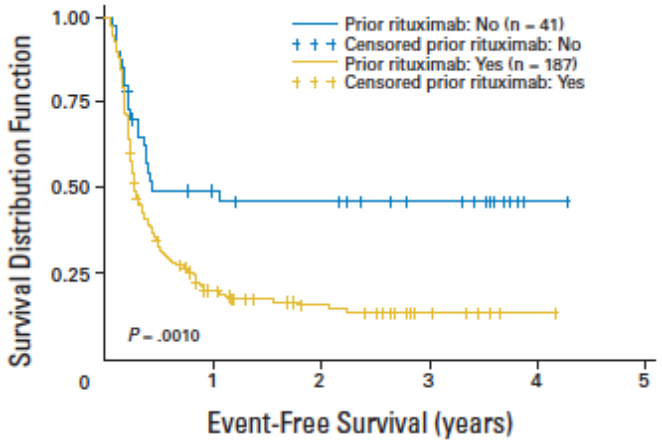
Crump, et al. JCO 2014

ORCHAARD



van Imhoff, et al. JCO 2017

CORAL



Gisselbrecht, et al. JCO 2010

- About 3/4 of DLBCL relapses happen within one year of frontline therapy
- Plus, only half of relapsed DLBCL patients are candidates for HDT/ASCT
- Chemo +/- ASCT fails the vast majority of patients with relapsed DLBCL today

Three randomized trials of Chimeric Antigen Receptor (CAR) T-cell therapy versus SOC in transplant-eligible DLBCL with early relapse or primary refractory disease

Clinical trials of CD19 CAR T-cell therapies in 2L ≤ 12 months LBCL

ZUMA-7[1]
(N = 359)
Phase 3; axi-cel vs SOC

Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD[4];

POSITIVE!

TRANSFORM[2]
(N = 184)
Phase 3; liso-cel vs SOC

TRANSFORM Study: Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase 3 TRANSFORM Study

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami

POSITIVE!

BELINDA[3]
(N = 322)
Phase 3; tisa-cel vs SOC

Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

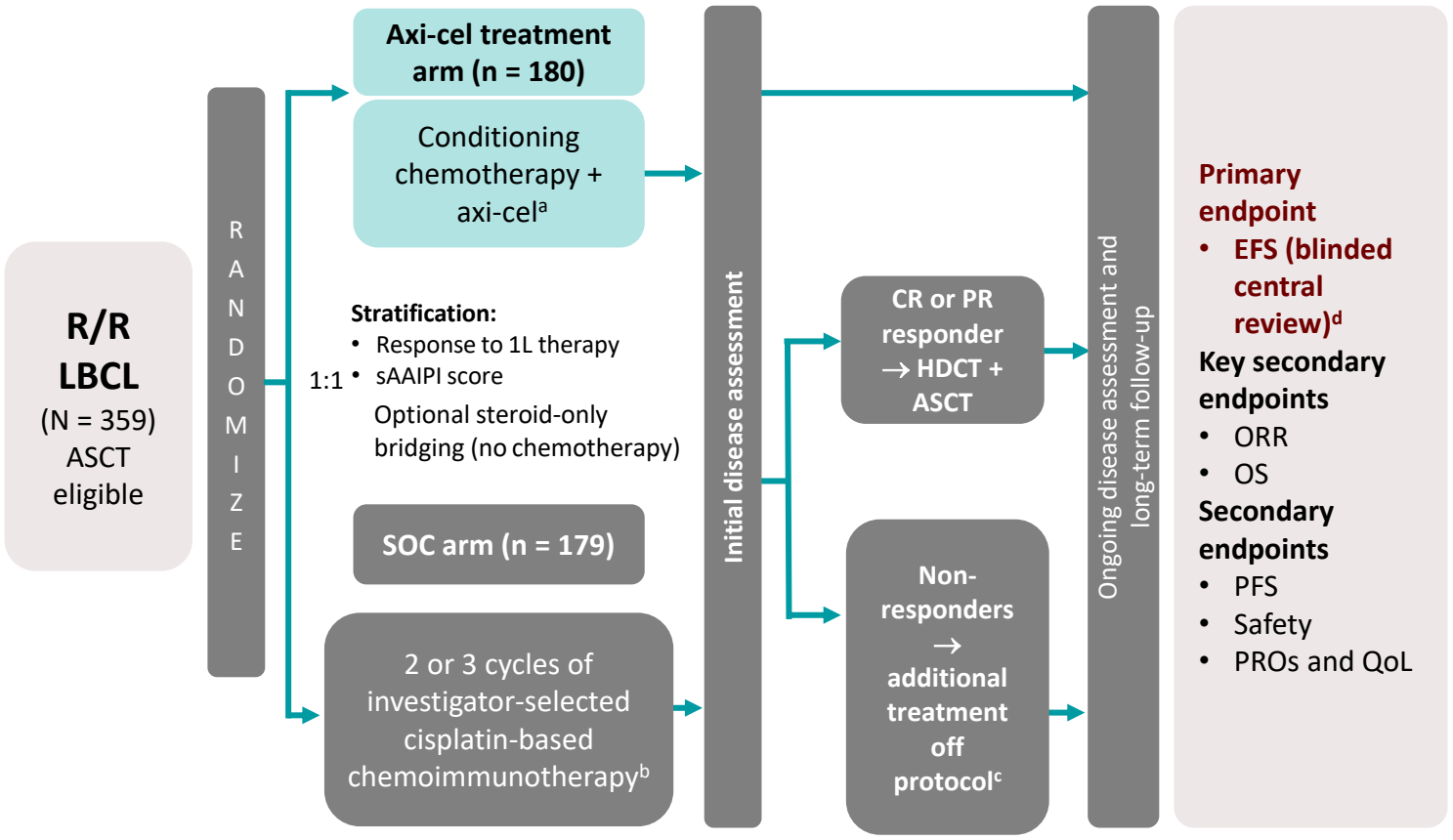
Michael R. Bishop,[1] Michael Dickinson[2], Duncan Purtill[3], Pere Barba[4], Armando Santoro[5], Nada Hamad[6], Koji Kato[7], Anna Sureda[8], Richard Greil[9],

NEGATIVE!

Inter-trial comparisons should not be made because of differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another.

1. Locke FL, et al. N Engl J Med. 2022;386:640-54. 2. Kamdar M, et al. Oral presentation at ASH 2021; abstract 91. 3. Bishop MR, et al. N Engl J Med. 2022;386:629-39.

ZUMA-7: axi-cel versus SOC in 2L LBCL



Characteristics	Axi-cel (n = 180)	SOC (n = 179)
Median age (range), years	58 (21–80)	60 (26–81)
Disease stage III-IV, n (%)	139 (77)	146 (82)
Primary refractory, n (%)	**133 (74)**	**131 (73)**
Relapse ≤ 12 months of 1L therapy, n (%)	**47 (26)**	**48 (27)**
HGBCL (incl. DHL/THL), n (%)	**31 (17)**	**25 (14)**
ECOG PS of 1	85 (47)	79 (44)
Elevated LDH level	101 (56)	94 (53)

Axi-cel has been approved by FDA for adult patients with LBCL that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy

Data cutoff: March 18, 2021.

[a] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with Cy (500 mg/m^2/day) and Flu (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2 × 10^6 CAR T cells/kg). [b] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [c] 56% of patients received subsequent cellular immunotherapy. [d] EFS was defined as time from randomization to the earliest date of PD per Lugano Classification. [e] Disease type according to central laboratory.

1L, first line; PRO, patient-reported outcome; QoL, quality of life; R-ESHAP, rituximab, etoposide, methylprednisolone, high-dose cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; sAAIPI, second-line age-adjusted International Prognostic Index; THL, triple-hit lymphoma.

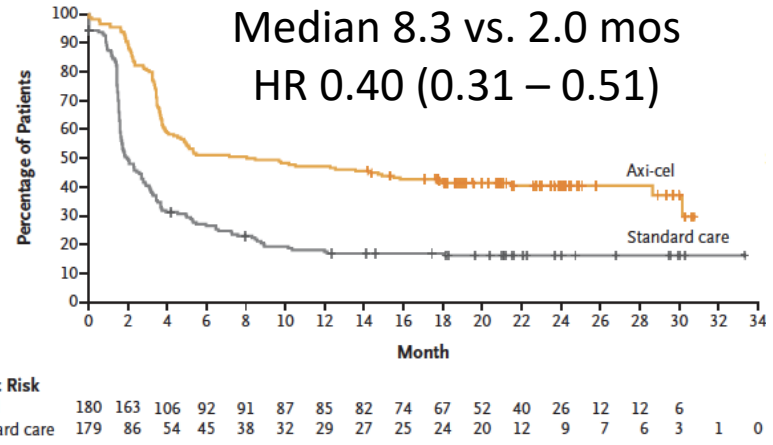
Locke FL, et al. N Engl J Med. 2022;386:640-54. Locke FL, et al. Oral presentation at ASH 2021; abstract 2. NCT03391466. Available from: https://clinicaltrials.gov/ct2/show/NCT03391466.

Axi-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas

ORR: 83% vs. 50%
CRR: 65% vs. 32%

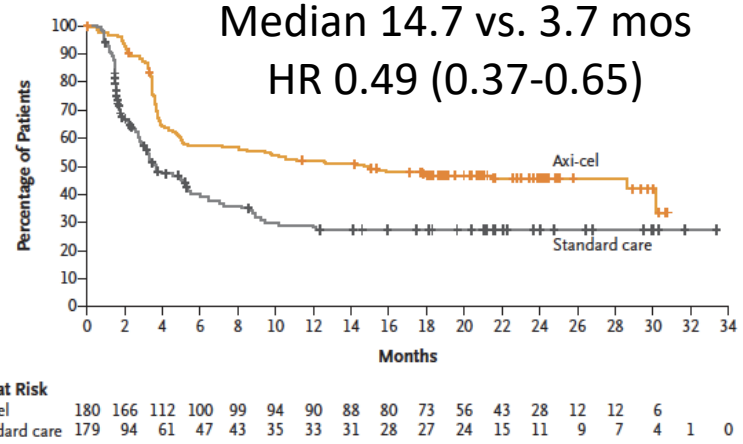
EFS

Median 8.3 vs. 2.0 mos
HR 0.40 (0.31 – 0.51)



PFS

Median 14.7 vs. 3.7 mos
HR 0.49 (0.37-0.65)



Toxicity	Grade	%
CRS	Any grade	92
	Grade 3-4	6
Neurotox	Any grade	60
	Grade 3-4	21

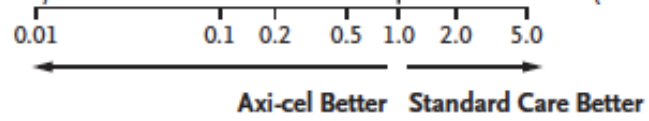
Median Follow-up: 24.9 mo

Axi-cel associated with improved QOL by PRO

Locke, et al. NEJM 2021

EFS improvements with axi-cel versus SOC were consistent among key patient subgroups

Subgroup	Axi-cel	Standard Care	(95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



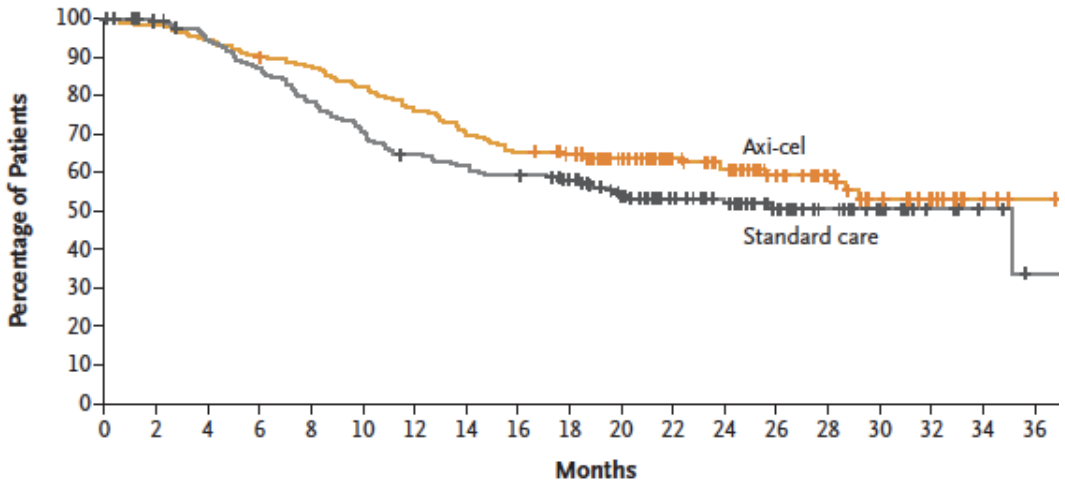
Locke FL, et al. N Engl J Med. 2022;386:640-54.

Overall Survival

OS

Median NR vs. 35.1 mos

HR 0.73 (0.53-1.01)



No. at Risk

Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2
Standard care	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1

March 21, 2023

Axi-cel CAR T-cell Therapy Demonstrates a Statistically Significant Improvement in Overall Survival for Initial Treatment of Relapsed/Refractory Large B-cell Lymphoma

-- First and Only Treatment in Nearly 30 Years to Show Statistically Significant Improvement in OS for Initial Treatment of R/R LBCL Patients Versus Historical Standard of Care in Curative Setting --

-- Landmark ZUMA-7 Study OS Data Reach Maturity Per Protocol, 5 Years After 1st Patient Randomized --

SANTA MONICA, Calif.--(BUSINESS WIRE)-- Kite, a Gilead Company (Nasdaq: GILD), today announced the primary overall survival (OS) analysis results of the Phase 3 ZUMA-7 study. The results showed a statistically significant improvement for axi-cel in OS versus historical treatment, which was the standard of care (SOC) in a curative setting for nearly 30 years, for initial treatment of adult patients with relapsed/refractory large B-cell lymphoma (R/R LBCL) within 12 months of completion of first-line therapy. Historical SOC is a multi-step process involving platinum-based salvage combination chemoimmunotherapy regimen followed by high-dose therapy (HDT) and stem cell transplant (ASCT) in those who respond to salvage chemotherapy. These findings will be presented in full later this year at an upcoming scientific meeting.

Locke FL, et al. N Engl J Med. 2022;386:640-54.

ZUMA-7 SOC Patients Who Received 3rd Line CAR T-cells

- 127 of 129 (71%) of SOC patients required 3rd line therapy

- 68 received 3rd line CAR T-cells
  - ORR 57%, CRR 34%
  - Median PFS 6.3 mos
  - Median OS 16.3 mos

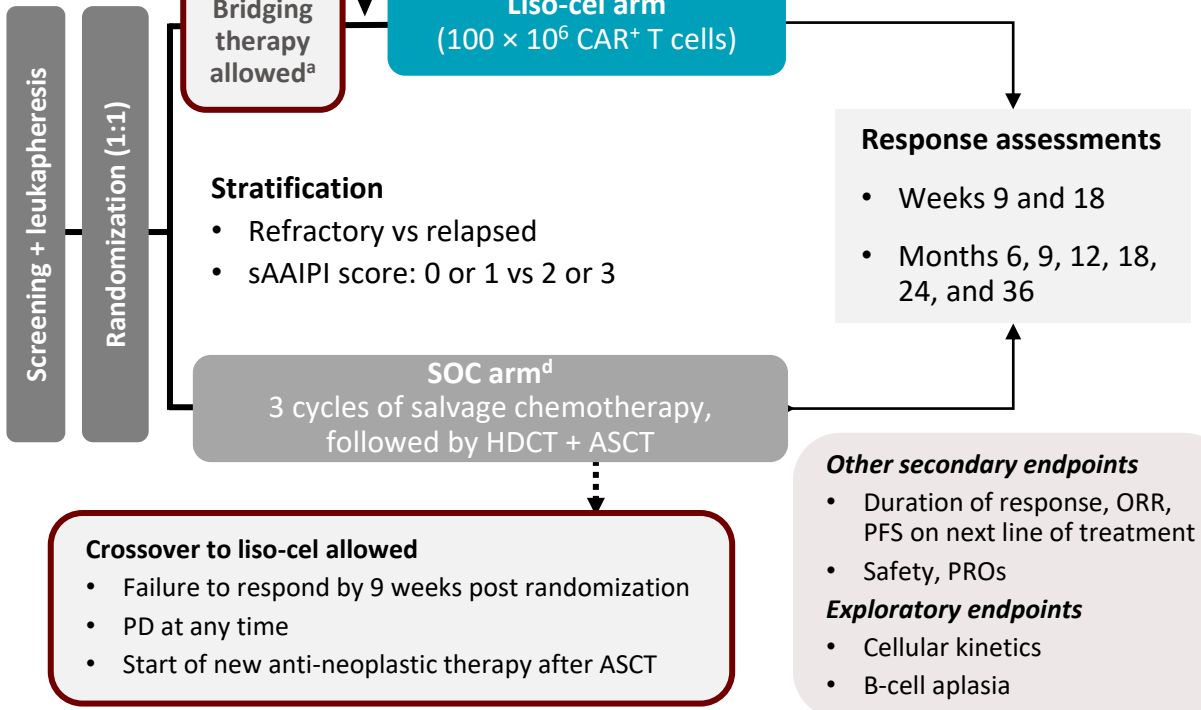
Efficacy of CAR T-cells is greater in patients randomized to receive them as 2nd line therapy

Ghobadi, et al. Proc. ASH 2022

TRANSFORM: liso-cel versus SOC in 2L LBCL

Key eligibility

- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from iNHL), HGBCL (DHL/THL) with DLBCL histology, grade 3B FL, PMBCL, THRBCL
- R/R ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS score ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum ALC



Primary endpoint:

- **EFS[e] (per IRC)**

Key secondary endpoints

- CRR, PFS, OS

Response assessments

- Weeks 9 and 18
- Months 6, 9, 12, 18, 24, and 36

Other secondary endpoints

- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints

- Cellular kinetics
- B-cell aplasia

Characteristic	Liso-cel (n = 92)	SOC (n = 92)
Median age (range), years	60 (53.5–67.5)	58 (42–65)
LBCL subtypes, n (%)		
DLBCL NOS	53 (58)	49 (53)
HGBCL (incl. DHL/THL), n (%)	**22 (24)**	**21 (23)**
PMBCL	8 (9)	10 (11)
DLBCL transformed from iNHL	7 (8)	8 (9)
Primary refractory, n (%)	**67 (73)**	**68 (74)**
Relapsed, n (%)	**25 (27)**	**24 (26)**
sAAIPI score, n (%)		
0 or 1	56 (61)	55 (60)
2 or 3	36 (39)	37 (40)
ECOG PS score of 1, n (%)	44 (48)	35 (38)

[a] Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing. [b] Only for patients who received bridging therapy. [c] Lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 days. [d] SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP. [e]EFS is defined as time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post randomization, or start of a new anti-neoplastic therapy, whichever occurs first. IRC, Independent Review Committee; LDC, lymphodepleting chemotherapy; LVEF, left ventricular ejection fraction; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Kamdar M, et al. Lancet 2022.

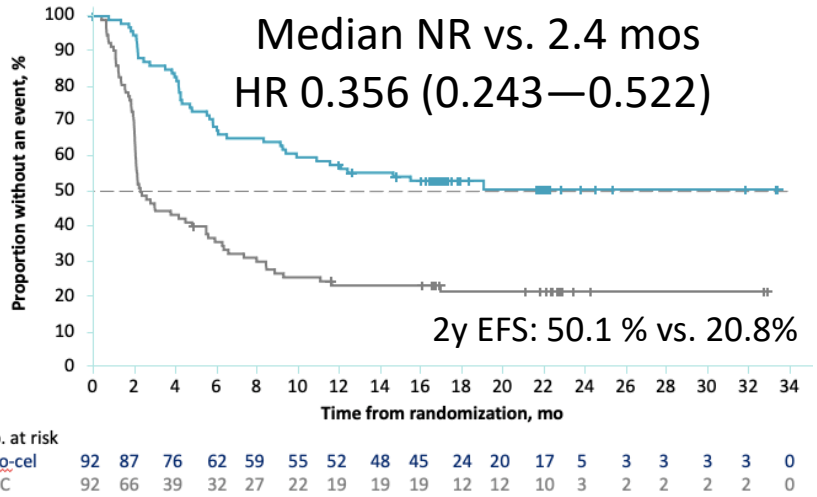
Liso-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas

ORR: 87% vs. 49%
CRR: 74% vs. 43%

66% of SOC pts crossed over

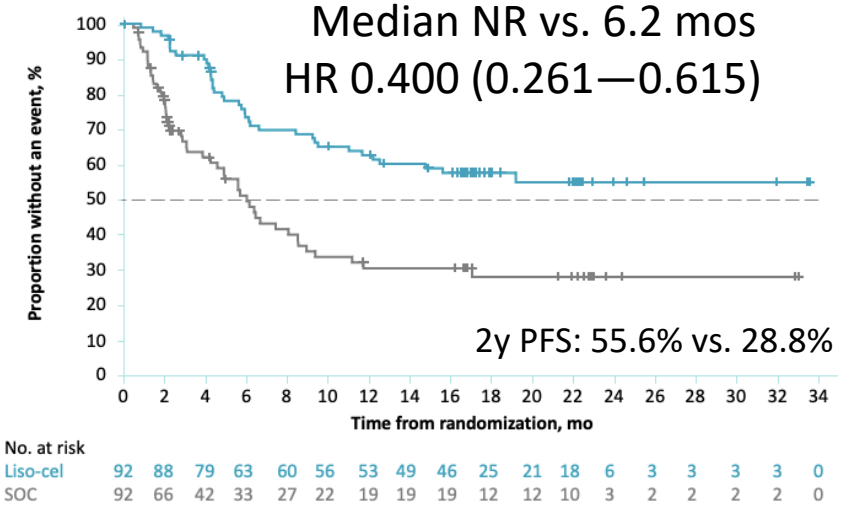
EFS

Median NR vs. 2.4 mos
HR 0.356 (0.243—0.522)



PFS

Median NR vs. 6.2 mos
HR 0.400 (0.261—0.615)



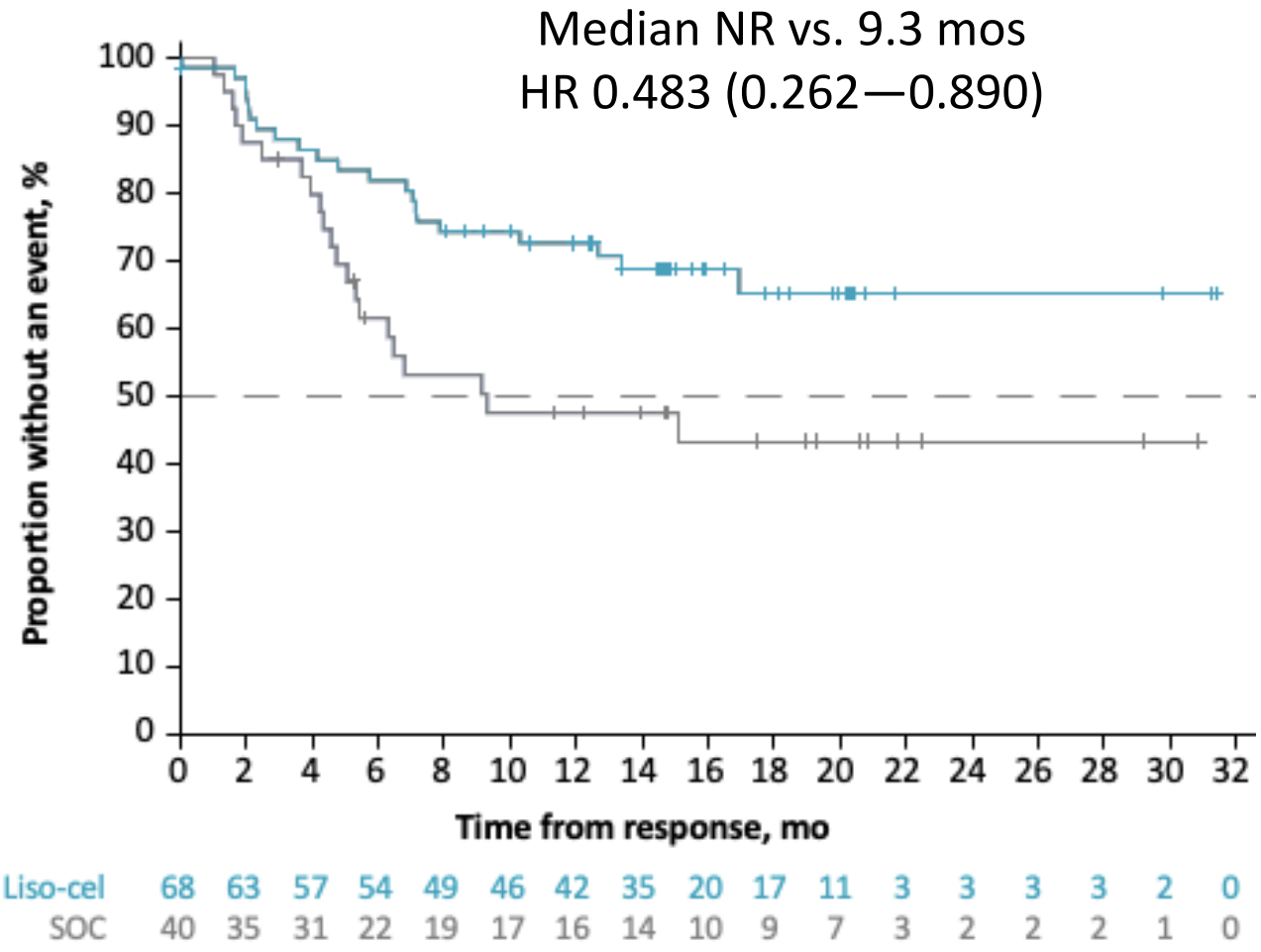
Toxicity	Grade	%
CRS	Any grade Grade 3	49 1
Neurotox	Any grade Grade 3	11 4

Median Follow-up: 17.5 mo

Liso-cel associated with improved QOL by PRO

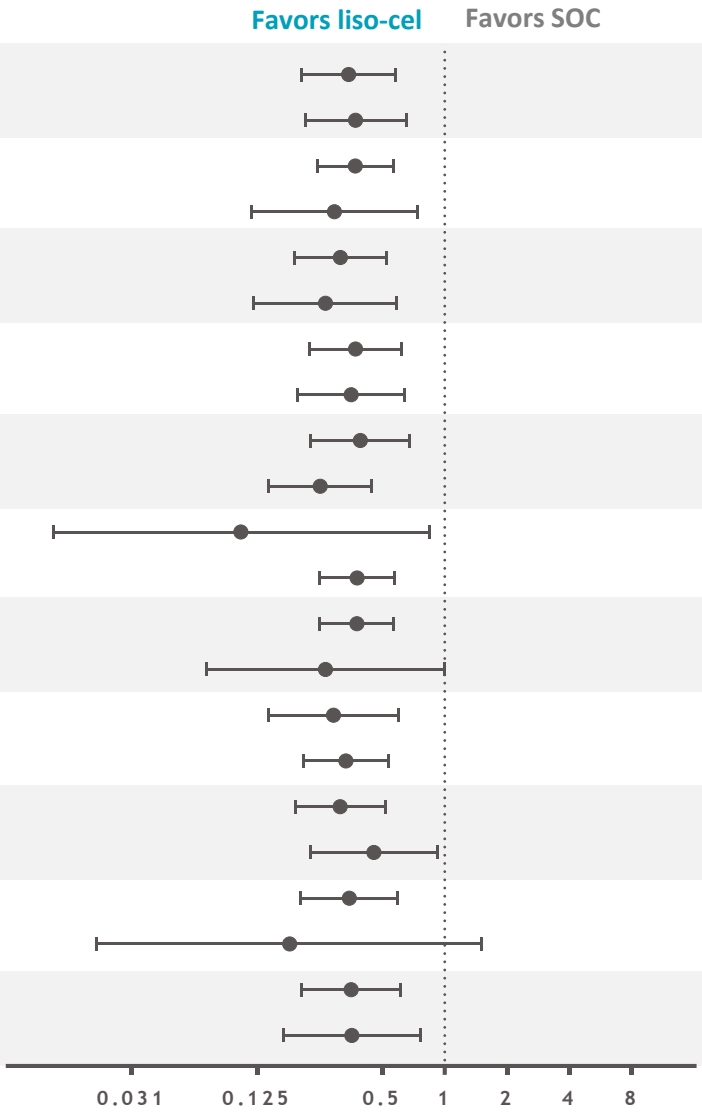
Abramson, et al. Blood 2023

Duration of Complete Response is Better with Liso-cel



Abramson, et al. Blood 2023

TRANSFORM: EFS per IRC by subgroup (ITT)



	Liso-cel, n/N	SOC, n/N	Stratified HR (95% CI)
sAAIPI: 0 or 1	23/56	39/55	0.34 (0.21—0.58)
sAAIPI: 2 or 3	21/36	32/37	0.37 (0.21—0.65)
Prior response status: refractory	37/67	57/70	0.37 (0.24—0.57)
Prior response status: relapse to last prior therapy	7/25	14/22	0.29 (0.12—0.74)
Age group, years: < 65	23/56	51/67	0.31 (0.19—0.52)
Age group, years: ≥ 65 to < 75	21/36	18/23	0.27 (0.12—0.59)
Sex: male	23/44	47/61	0.37 (0.22—0.62)
Sex: female	21/48	24/31	0.35 (0.19—0.64)
ECOG PS (at screening): 0	20/48	40/57	0.39 (0.23—0.68)
ECOG PS (at screening): 1	24/44	31/35	0.25 (0.14—0.44)
SPD: > 50 cm^2	3/10	9/10	0.10 (0.01—0.85)
SPD: ≤ 50 cm^2	38/77	59/76	0.38 (0.25—0.57)
Lactate dehydrogenase: < 500 unit/L	38/79	60/81	0.38 (0.25—0.57)
Lactate dehydrogenase: ≥ 500 unit/L	5/10	11/11	0.27 (0.07—1.00)
Prior CT response status: chemorefractory (PD, SD)	18/26	17/18	0.29 (0.14—0.60)
Prior CT response status: chemosensitive (PR, CR)	26/66	54/74	0.33 (0.21—0.54)
NHL type: DLBCL	25/60	46/58	0.31 (0.19—0.52)
NHL type: HGBCL	18/22	18/21	0.46 (0.23—0.92)
DLBCL subtype: DLBCL NOS de novo	23/53	39/50	0.35 (0.20—0.59)
DLBCL subtype: DLBCL transformed from indolent NHL	2/7	7/8	0.18 (0.02—1.51)
DLBCL subtype based on cell of origin: GCB	27/45	32/40	0.35 (0.21—0.61)
DLBCL subtype based on cell of origin: ABC, non-GCB	10/21	26/29	0.36 (0.17—0.76)

CT, chemotherapy; SD, stable disease; SPD, sum of the product of perpendicular diameters.

Abramson JS, et al. Blood 2023

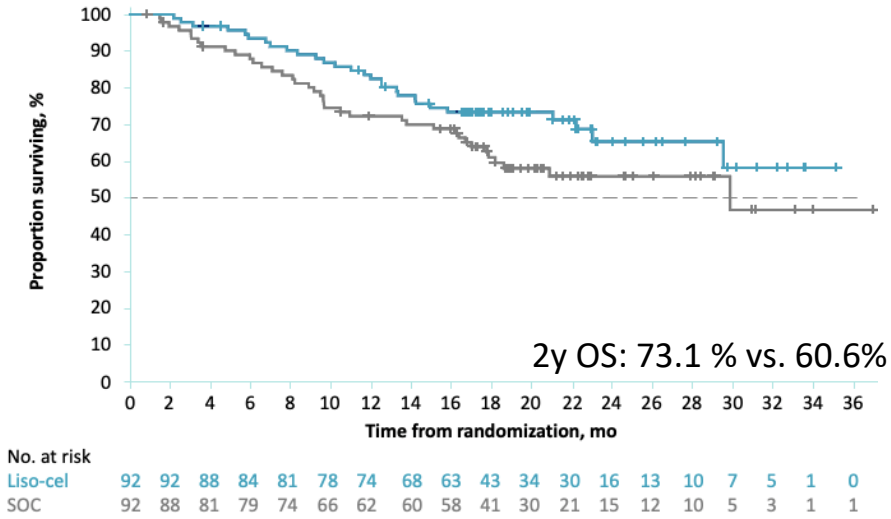
TRANSFORM: Primary Mediastinal B-cell Lymphoma

	Liso-cel (n=8)	SOC (n=9)
Overall Response Rate	8 (100%)	3 (33%)
Complete Response Rate	8 (100%)	3 (33%)
Event-free survival, median Event-free survival, 18 m	NR 87.5%	2.2 m 33%

Liso-cel vs. SOC as 2nd line therapy: Overall Survival and Crossover

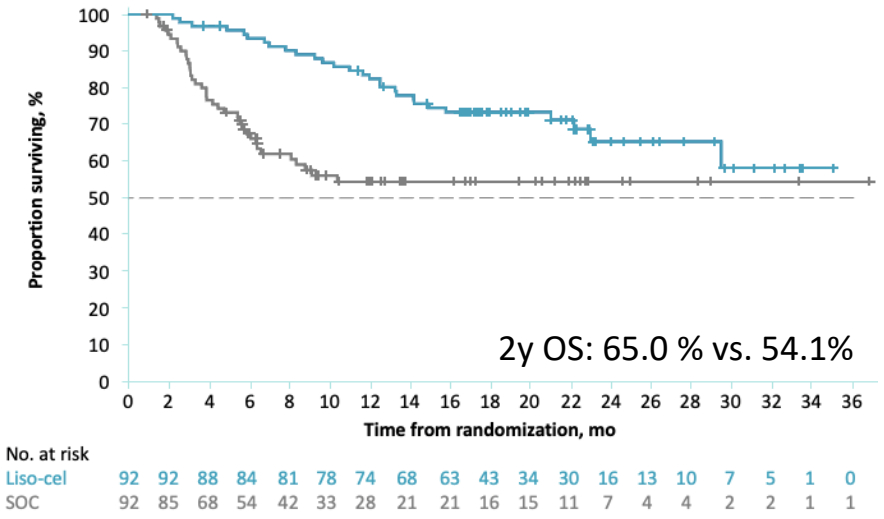
OS

Median NR vs. 29.9 mos
HR 0.724 (0.443—1.183)



OS adjusted for crossover

Median NR vs. NR
HR 0.415 (0.251—0.686)



Crossover subgroup

N=61 (66% of SOC)

	Crossover subgroup (n = 57 treated)
Median time from crossover to infusion	15 days (range 12-26)
Median f/u	12.0 m (1.4—28.1)
ORR / CRR	61% / 53%
Median EFS	5.9 m (3.1—15.1)
Median PFS	5.9 m (3.2—26.5)
Median OS	15.8 m (11.8—NR)

Median Follow-up: 17.5 mo

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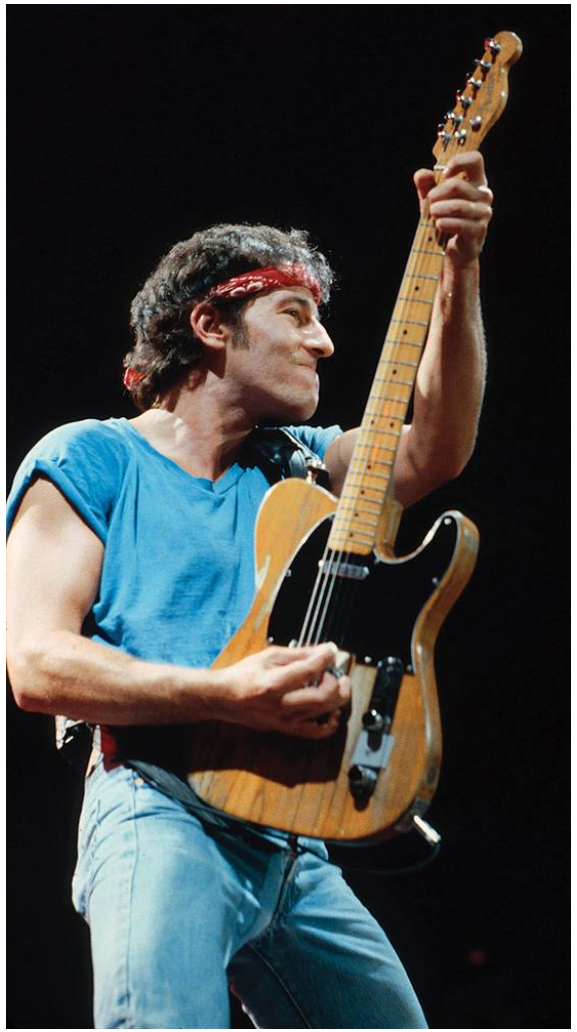
Why use CAR over chemotherapy +/- ASCT in 2nd line?

- CAR T-cells **CURE MORE PATIENTS**!
- Only 16% of SOC patients on ZUMA-7 remained event free at 2 years!
- Patients (and their T-cells) are more beat up after failing 2nd line chemotherapy, and may not be able to get to CAR T-cells in the 3rd line setting
- Patients receiving 3rd line CAR after failing SOC on TRANSFORM and ZUMA-7 **didn't do as well** as patients getting CAR 2nd line
- **Overall survival is emerging in favor of CAR** over SOC in both ZUMA-7 and TRANSFORM despite having CAR T-cells as a 3rd line therapy

2nd line ASCT in DLBCL? Not in the CAR era (for most patients)!

The 80s rockers can still bring it when needed *(young fit pts with late relapse, but this is a small group)*



Since the 80s, even Mr. T has evolved

Thank you for your attention!

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